Efficacy and Safety of Sri Lankan Traditional Medicine Regimen for Knee Osteoarthritis: Study protocol for an open label randomized controlled trial

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Abstract

Background

Osteoarthritis (OA) has become a burden globally for the healthcare sector due to its high prevalence and incidence. Among that Knee Osteoarthritis (KOA) is the most common form of arthritis causing disability and impaired quality of life especially in elderly. Currently pharmacological, non-pharmacological and surgical measures are considered in treatment of OA with aims of reducing pain and improving function of the knee joint but currently there is no known cure and no interventions available to stop the progression or manage the symptoms with an acceptable benefit to harm profile. Traditional and Complementary Medicine (T&CM) is used not only to treat diseases, especially chronic diseases like OA, it is also widely used in disease prevention, health promotion and health maintenance, and it has proved to be cost effective for some governments. In Sri Lanka, Sri Lankan Traditional Medicine (STM) which is probably the oldest form of treatment used in the country specially for joint related disorders including OA. STM regimens are widely used to treat OA but no clinical trial evaluated on STM regimens for KOA to discuss their safety and efficacy in the treatment of KOA but most of the clinical trials evaluated on herbal preparations as single interventions. The aim of this study is to compare the efficacy and safety of Sri Lankan Traditional Medicine Regimen which include a decoction, pill, herbal fomentation and a paste for Knee Osteoarthritis in comparison to recommended conventional pain management therapy over a period of 8 weeks on relieving the condition of KOA.

Study Design

This is a two months clinical trial following a protocol driven open labeled randomized controlled study enrolling patients with KOA.

Rasnadvigunabhagasaya decoction (RDBD) prepared from parts of 26 different plants that are used in traditional medicine for a variety of purposes such as reduction of pain, reduction of inflammation, and antipyretic activity, is one of the test products. While administrating internally, usually it was advised to given along with ginger powder or long pepper powder or with Yogaraja Guggulu or Ajamoda powder or castor oil. *Yoaraja Guggulu was selected for this study* as the recue medication *based on its frequent usage in Sri Lankan Traditional Medicine for treating joints disorders* it was which was co prescribed for the Rasnadvigunabhagasaya decoction. The efficacy and safety of the two Ayurvedic dosage forms will be tested against the non-steroidal anti-inflammatory drugs (NSAIDS) Tab Paracetamol and Tablet Ibuprofen as the rescue medication. As test products for external application, two preparations were selected from rewritten ola leaves and print as Thalpathe Pillium Book Series. The form of fomentation (Thevili Pottani with Oil application) contained 10 ingredients of herbal ball and dip in five types of oil mixture (Pasthel): Kumburuetaperumkayam Pottani (KAP) and paste (Paththu/Lepa): Sandivadam Lepaya (SVL) consist of 15 ingredients were selected. The efficacy and safety of these two external applications will be tested against the Diclofenac sodium gel and hot water fomentation. Patients with symptoms of Knee OA will be allocated randomly into two arms and the medications will be given orally for 60 days and externally for 30 days. The primary endpoint is a change in the score on the Western

Ontario and McMaster University Osteoarthritis Index (WOMAC) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) after 12 weeks. WOMAC and KOOS will be recorded and compared between the two arms prior to visit 1, at the end of 15 days and end of 30 days, and end of the 45 days and end of second month and three months of follow- up. WOMAC subscales, a pain disability index, a visual analog scale for pain and sleep quality, a quality-of-life index are used as secondary outcome measurements.

Discussion

This clinical trial will be able to provide evidence based scientific data on Sri Lankan Traditional Medicine regimen, RDBD with Yogaraja Guggulu, KAP and SVL in the management of Knee OA. This trial is expected to develop capacity to scientifically evaluate various Sri Lankan traditional Medicines that are claimed to have efficacy in treatment of various disease conditions.

Trial Registration

ISRCTN58050062: https://doi.org/10.1186/ISRCTN58050062

Background

Osteoarthritis (OA) has become a burden globally for the healthcare sector due to its high prevalence and incidence. Among that Knee Osteoarthritis (KOA) is the most common form of arthritis causing disability and impaired quality of life especially in elderly (1). The WHO report on priority diseases and reasons for inclusion 2018, provides an in-depth review of the various diseases or conditions including osteoarthritis in its chapter sixth has been selected and grouped according to the nature of the pharmaceutical gap(s) associated with it (2). Osteoarthritis Research Society International (OARSI) also identified OA as a serious disease and one of their major concerns is treatments for osteoarthritis (3).

Prevalence of knee pain has been reported as 25–56%, and appears to vary according to geographical location. Prevalence of knee pain in the US has increased by 65% between 1983 and 2005, in Germany citizens aged 40 years and older 30.9% reported knee pain and Swedish adults' age 58 - 84yrs, the prevalence of frequent knee pain was 25.1%. China reported the prevalence of knee pain of 44% in men and 56% in women aged 59 years and above (4).

In India Osteoarthritis is the second most common rheumatologic problem and prevalence of 22–39% (5). OA accounts for 24% of all years lived with disability (YLD) and has been ranked as the 10th leading contributor to global YLDs. The economic burden of arthritis on patients and society is high in every country that it has been estimated and job-related indirect costs due to loss of productivity have been estimated to cost from $ 3.4 to $ 13.2 billion per year. Recent guidelines have addressed the many treatments that aim to relieve symptoms, in particular pain and improved function, and not provide a cure for OA. The treatments that are available for the management of OA have adverse effects that are not significant. There are numerous drug treatments for osteoarthritis; however, their efficacy and adverse effect profiles often limit their use. Currently pharmacological, non-pharmacological, and surgical

measures are considered in the treatment of OA with aim of reducing pain and improving the function of the knee joint and currently there is no known cure and no interventions available to stop the progression or manage the symptoms with an acceptable benefit to harm profile (6).

Sri Lankan Traditional Medicine (STM) called *Desheeya Chikitsa*, which is probably the oldest form of treatment used in the country and use of STM in health maintenance and in disease prevention and treatment, particularly for chronic diseases like KOA. By reviewing most diseases and disease conditions related to OA: *Sandhi Vadam, Janu Gada* and *Sandhigata Vata* are frequently used in classification of diseases stated in STM under the disease category of *Vata Roga* (8–9). For this condition there are many treatment regimens including decoctions, pills, pastes and fermentation procedures etc; recorded which would be efficacious for long term management (7 - 21). Despite the importance of the OA issue, this topic has not yet been addressed in any great depth in the field of STM. Most of the clinical trial evaluated on herbal preparations as single interventions, STM regimens are widely used to treat OA but no clinical trial evaluated on STM regimens for KOA to discuss their safety and efficacy in the treatment of KOA (22).

Individual STM treatment regimens for *Sandivadam* included a specific treatment types which often require the individual to take an active part in their own treatment at home with general and specific STM life style modification measures and nutritional advices. With less invasive non hospitalized procedures and low cost but efficacious methods unnecessary to take leave from their current occupation and ingredients used to prepared drugs were well established with research findings and freely available in Sri Lankan Settings. Hence this study considered the common STM regimen standards of practice, decoctions and pills are therapies by far the most used medicines internally. *Rasnadvigunabhagasaya* decoction which includes 26 ingredients, is an herbal decocotion indicated effective in reducing pain in *Sandhigata Vata*, and advised to take *Yogaraja Guggulu* with this decoction used as the internal medicines and the form of fomentation (*Thevili Pottani with Oil application*) contained 10 ingredients of herbal ball and dip in five types of oil mixture (*Pasthel*): *Kumburuetaperumkayam Pottani* (KAP) and paste (*Paththu/Lepa*): *Sandivadam Lepaya* (SVL) consist of 15 ingredients were selected for external use as local application in this study. No scientific studies have been published that have evaluated the efficacy and safety of the above-mentioned Sri Lankan traditional treatment regimen for Knee OA. Therefore, this study will evaluate the efficacy and safety of the aforesaid Sri Lankan Traditional medicine regimen in comparison to the non-steroidal anti-inflammatory drugs (NSAIDS) Tab Paracetamol and Tablet Ibuprofen internally and external application of Diclofenac sodium gel and hot water fomentation used in an allopathic system in patients with symptoms of Knee OA.

Method

Study design

This is a two months clinical trial following a protocol driven open labeled randomized controlled study that will be conducted at the National Ayurveda teaching hospital in Borella, Colombo, Sri Lanka. RDBD

and Yogaraja Guggulu internally, KAP and SVL externally used in Sri Lankan traditional medicine as a regimen for knee OA will be the test products. The efficacy and safety of this regimen will be tested against the non-steroidal anti-inflammatory drugs (NSAIDS) Tab Paracetamol and Tablet Ibuprofen internally and external application of Diclofenac sodium gel and hot water fomentation. Patients with symptoms of Knee OA will be allocated randomly into two arms after a 1 week run – in period and the medications given orally for 60 days and externally for 30 days. This study protocol was developed as required by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Additional file 1).

Ethics approval has been obtained from the ethics Review Committee, Institute of Indigenous Medicine (ERCIIM), University of Colombo, Sri Lanka (ERC /20/105). The trial was registered in the ISRCTN registry (Trial number ISRCTN58050062) (Additional file 2)

Study Setting

The study will be conducted in the National Ayurveda Teaching Hospital, Borella, Colombo, Sri Lanka and Institute of Indigenous Medicine (IIM), University of Colombo, Rajagiriya, Sri Lanka. The study subjects will be recruited from the patients with symptoms of knee OA who visit to the Out Patient Department (OPD) of National Ayurveda Teaching Hospital and those who come responding to a newspaper advertisement on trial requirement.

Participants

Patients will be selected from those who seeking treatment for Knee OA. Participants in this research project is voluntary. Recruitment is done by screening for eligibility criteria (Inclusion and exclusion criteria). Eligible subjects will be randomly assigned to the Sri Lankan Traditional medicine regimen and the conventional treatment regimen group.

Inclusion Criteria and Exclusion Criteria

The inclusion criteria

Diagnosis of KOA will be based on history, clinical examination findings and classical radiological findings (ACR functional class I, II or III); and fulfilling the American College of Rheumatology (ACR) classification criteria except that the lower age limit was reduced to 40 years; and Radiographic evidence of OA will be based on the ranking score of the Kellgren-Lawrence radiographic system and pain severity will be based on VAS.

1. Three American College of Rheumatology (ACR) classification criteria for knee will be used. They are including:

1.1. The ACR Clinical classification criteria of knee OA

1.2. The ACR Clinical/Radiographic classification criteria of knee OA

1.3, The ACR Clinical/Laboratory classification criteria of knee OA

1.1. The ACR Clinical classification criteria for knee OA

In this criterion the presence of knee pain along with at least three of the following six items can classify the knee OA in the patients

- Age> 50 years old
- Morning stiffness < 30 minutes
- Crepitus on knee motion
- Bony tenderness
- Bony enlargement
- No palpable warmth

1.2. ACR Clinical/Radiographic classification criteria,

The presence of knee pain with at least one of the following three items along with osteophyte in knee X-Ray can classify the knee OA in the patients:

- Age> 50 years old
- Morning stiffness < 30 minutes
- Crepitus on knee motion

1.3. ACR Clinical/Laboratory classification criteria

The presence of knee pain along with at least 5 of the following 9 items can classify the knee OA in the patients:

- Age> 50 years old
- Morning stiffness < 30 minutes
- Crepitus on knee motion
- Bony tenderness
- Bony enlargement
- No palpable warmth
- RF < 1 40
- Synovial fluid compatible with OA

1. Pain Visual Analogue Score
2. A five-point Liker it scale version with five response levels for each item, representing different degrees of intensity: None (0), mild (1), moderate (2), severe (3), and extreme (4). The maximum score is 10 points for pain, Higher scores indicate more or worse symptoms, maximal limitations,

and poor health. The patients will have reported a mean pain intensity in one or both knees while performing a weight bearing activity (e.g. walking, standing, climbing staircase) of ≥40 mm on a 100 mm Visual Analog Scale over the 7 days before baseline assessment, and provide written informed consent.

3. Radiographic evidence of OA

This will be assessed on the ranking score of the Kellgren-Lawrence radiographic system (0-4) and 1- 3 grades will be considered.

Exclusion Criteria

1. Subjects who have non-degenerative joint diseases or other joint diseases such as rheumatoid arthritis, psoriatic arthritis, gonococcal arthritis and haemoarthritis;
2. Subjects with severe disabling arthritis and / or the patient are bedridden;
3. Those that had history of intra-articular knee injection within the month preceding the study;
4. Those with evidence of severe unstable renal, hepatic, diabetic, haemopoietic, cancer, hypertensive, cardiac disorder and mentally affected as revealed by history and / or investigation.
5. concurrent anti-coagulant/antiplatelet drugs, corticosteroids or narcotic pain killers use; history of epilepsy or bleeding disorders; gastric ulcers; renal or hepatic disease; uncontrolled hypertension, or body mass index (BMI) >45 kg/m2.

A washout period of 7 days was required for NSAIDs users. Discontinuing the use of common CAM therapies for arthritis (e.g., glucosamine, chondroitin sulfate, bromelain, DMSO (*DiMethyl SulfOxide),* acupuncture and Ayurveda medicine) was required for 7 days prior to enrollment.

Sample Size

Sample size was calculated based on the primary outcome measurement of in WOMAC Index 10- point improvement of score from baseline after 12 weeks between both parallel groups of the clinical trial. This study is designed to evaluate the comparative clinical efficacy and safety of the Sri Lankan Traditional Medicine regimen with the conventional treatment regimen, assuming a parallel-group design between the two interventions. The sample size was calculated as specified by Kessler et al (22). According to a previous study done among patients with knee OA using Ayurveda treatment Regimen, clinically significant 12 weeks conventional

treatment response in about 30%, therefore the clinically important difference of 0.3 compared to the active drug is considered to be acceptable. The sample size was calculated for a significance level (α) of 5% and power of 80%. The sample size calculated using these values is 39 per group. With an expected dropout rate of 10%, the minimum sample size was calculated as 43 for one arm.

Recruitment of Patients

People who are interested in participating in this clinical study will be provided with a detailed Information sheet supplemented by verbal explanation of the study procedures. If the participants agree with the information given, the screening questionnaire will be completed. Informed written consent will be obtained from each participant by the investigators prior to initial interview. The activities in the initial interview will include complete history taking, physical examination, and hematological and biochemical investigations (FBS, FBC, ESR, ALT/AST, serum creatinine, UFR). Diagnosis of Knee Osteoarthritis will be made according to history, clinical examination findings and classical radiological findings (ACR functional class I, II or III); and fulfilling the American College of Rheumatology (ACR) classification criteria and Radiographic evidence of OA will be based on the ranking score of the Kellgren-Lawrence radiographic system and pain severity will be based on VAS. Among them, the participants meeting the inclusion and exclusion criteria will be recruited for the study. All baseline assessment forms (WOMAC, KOOS and VAS) will be completed by the investigators. Patients will not be allowed to take any other medicines during the trial period. If they have to take any other medicine, they should inform the investigators and discontinue the trial.

Baseline Assessment

WOMAC, KOOS and VAS and heamatological and biochemical investigations (FBS, FBC, ESR, CRP, ALT/AST, serum creatinine, EGFR, UFR, Lipid Profile) will be assessed at baseline.

Randomization

Randomization sequence will be generated using an online randomization website (www.randomisation.com). Block randomization will be done using blocks of 10 to generate the randomization schedule for 86 patients. The patients will be allocated to treatments based on the randomization sequence generated. Two week's supplies of the assigned investigational products will be handed over to the patients according to the randomized allocation. Each group will be enrolled with an allocation ratio 1:1. The allocation for each randomization number will be put in to individually seal opaque envelops. The envelopes and allocation sequence will be kept under lock and key by one investigator not involved in recruiting patients. The patients meeting inclusion exclusion criteria and recruited into the study will be assigned a randomization number sequentially, according to the date and time of recruitment. The allocated treatments indicated in the sealed envelope for each randomization number will be supplied to each patient.

To monitor compliance and adverse events, two weekly follow up will be done at the Borella Ayurveda Teaching Hospital. The trial will be registered at clinical trial registry and approval will be taken by the University ethics committee. It will be followed the Declaration of Helsinki and Good Clinical Practice guidelines for trial conduct.

Participants will be assigned in the open labeled study and provided written informed consent before taking part for 8 weeks of regimen 1 (Arm I) or regimen 2 (Arm II). Outcomes will be assessed by weekly

follow up at the Borella National Ayurveda Teaching Hospital and each assessment detail of the outcome study will be informed to the participant. The study design flow chart is shown in Fig.1.

Intervention

Investigational products

Sri Lankan Traditional Medicine Regimen

Product I - Rasnadvigunabhagasya Decoction (RDBD) and Yogaraja Guggulu

Traditional RDBD is a brown – colored liquid, prepared using 80g *Alpinia calcarata* and 1.6g other 24 plant ingredients: *Tragia involucrate, Sida cordifolia, Ricinus Cummunis, Cedrus deodara*, *Curcuma zedoaria, Crocosmia aurea*, *Justicia adhatoda, Zingiber officinale, Terminalia chebula, Piper chavya, Cyperus rotundus, Boerhavia diffusa, Tinospora cordifolia, Argyreia populifolia, Anethum sowa, Tribulus terrestri, Withania somnifera, Aconitum heterophyllum, Cassia fistula, Asparagus racemosus, Piper longum, Nilgirianthus ciliates, Coriandrum sativum, Solanum indicum.* The dried plant materials of the 25 ingredients will be ground separately to pre-prepare a coarse powered pack welighing 120g containing 25 ingredients. 120-g of dried powder pack of decoction will be used to prepare the decoction needed for 2 days. A two-week supply (Seven packs) of these pre- prepared dried herbs pack will be supplied to the patient. They will be informed to put the supplied herbal pack into an earthen pot or stainless-steel pot, add 3840 ml of water and simmer under low flame until the volume is reduced to 480 ml. The process of preparation under standard conditions will be demonstrated to the patients who are selected into the RDBD arm at the Department Dravyaguna Vignana or Department of Kayachikithsa of IIM using video. They will be requested to take a daily dose 120 ml of decoction before breakfast (6am) and before dinner (6pm) daily rest for the next day before breakfast (6am) and before dinner.

2 pills of Yogaraja Guggulu will be purchased from Sri Lanka Drug cooperation and Ayurveda Drug cooperation and will 56 pills will be packed in light and waterproof polythene provided which be requested to take along the decoction for rescue pain.

Product II - Sandhi Vadam Lepaya (SVL)

Pastes or Lepa or Paththu will be prepared according to the standardized and quality-controlled methods described in Sri Lankan Traditional Medicine. Paththu will be given for the external application on Knee prepared by 15 ingredients: *Asparagus racemosus* (Both tube and leaves) 50g, *Crataeva nurvala* (Leaves and Bark) 50g, *Moringa oleifera* (Bark) 50g, *Vitex negundo* (Leaves and Bark) 50g, *Caesalpinia bonduc* (Leaves and Bark) 50g, *Alstonia scholaris*(Bark) 50g pounded well and take 1920ml juice after squeezing and heated upto 480ml. *Piper nigrum* (Fruit) 10g, *Allium sativum* (Bulb) 5g, *Zingiber officinale* (Rhizome) 5g, *Pipper longum*(Fruit) 5g, *Ferula asafoetida* (Resin) 5g, *Trachyspermum ammi*(Seeds) 5g, *Cuminum* cyminum (Seeds) 5g, *Caesalpinia bonduc* (Seeds) 5g grounded separately and grinded with *lime juice* and add it to 240ml of lime juice and mixed well. Add this mixture to the previously prepared juice and keep it in flame until turn thick by evaporating its water content. One packet of 50g in light and

waterproof packed will be provided to use for one day. 14 packets will be provided for evenly applied over the knee it should be covered with a cotton wool and properly bandaged with a gauze bandage. Keep it for 8hrs and removed and ask to cleanse the knee area properly.

Product III – Kumburuatadi Pottaniya (KAP)

Herbal fomentation bollus (Pottaniya) prepared with 10 ingredients: *Caesalpinia bonduc*(Seed Pulp) 7.5g, *Ferula asafoetida*(Resin) 7.5g, *Zingiber officinale* (Rizome) 7.5g, *Pipper longum* (Fruit) 7.5g, *Allium sativum* (Bulb) 7.5g, *Terminalia chebula* (Fruit) 7.5g, *Maduka Indica* (Seed) 7.5g, *Ricinus communis* (Seed) 7.5g, *Sesamum indicum* (Seed) 7.5g, *Cococus nucifera* (Seed pulp) 7.5g Taken and pounded well and make a pollute and steam it. Dip in a heated mixture of oils of Mee thel (Oil extracted from seeds of *Maduka Indica*), Erdu thel (Oil extracted from seeds of *Ricinus communis*), Thala thel (Oil extracted from seeds of *Sesamum indicum*), Elagithel (Ghee) and Polthel (Oil extracted from seed pulp of *Cococus* nucifera) collectively known as Pasthel (Five types of Oils) used commonly in Sri Lankan Traditional Medicine. Two pottani will be given to the patient and they will be informed to steamed properly and dip in lightly heated mixture of 5ml oil from each above mentioned five oils (Mee, Eradu, Thala, Ethagithel and Pol thel) and fomentation done for 30 min after removing the paste.

Product IV - Tablet Paracetamol and Tablet Ibuprofen

Individualized conventional care for knee OA according to current practices, Non-Steroid Anti-Inflammatory Drugs (NSAIDs) - Paracetamol (500mg) and Ibuprofen (200mg) as rescue medication were selected as the comparator for this clinical trial. Total quantity of Paracetamol and Ibuprofen required for clinical trial, from one of the leading brands of paracetamol and Ibuprofen will be purchase from one single batch, directly from the State Pharmaceutical Company (SPC) for the purpose of the trial. The purchased products will be stored under the 25^0 C in an air- conditioned environment at the IIM. Patients allocated to conventional arm are requested to take a daily dose of two tablets of Paracetamol (500mg) and two tablets of Ibuprofen (200mg) twice a day after breakfast and after dinner

Product V - Diclofenac Sodium gel and fomentation with warm water

Topically applied NSAIDs reduce systemic exposure compared with oral NSAIDS, and European guidelines recommend their use. The NSAID is available in a range of topical formulations. Topical formulation of 2% Diclofenac Sodium gel aims to reduce adverse systemic problem and fomentation with warm water recommended before applying it. Total quantity of 2% Diclofenac Sodium gel required for clinical trial, from one of the leading brands of 2% Diclofenac Sodium gel will be purchase from one single batch, directly from the State Pharmaceutical Company (SPC) for the purpose of the trial. The purchased products will be stored under the 25^0 C in an air- conditioned environment at the IIM. Patients allocated to conventional arm are requested to applied 2% Diclofenac Sodium gel over knee and carried fomentation with warm water once a day.

Details of the investigational drugs are shown in Table 1. To minimize the compliance, patients are advised to submit the patient's diary and empty containers of the drugs during weekly visits. Also, the day before the clinic date of every week, the chief investigator will be telephoned and send a text message to a mobile phone to be reminded of the clinic date.

Table 1 Investigational Products

Treatment Regimen	Treatment Duration	Interventional Group – Arm I	Conventional Group Arm II
External Thermotherapy	30 days	Fomentation (pottani) – KAP 100gms daily	Hot water Sufficient amount daily
Topical Application	30 days	Paste – SVL Necessary Amount daily	2% Diclofenac sodium gel Sufficient amount daily
Internal	60 days oral	Rasnadvigunabhagasya Decoction – RDBD 120ml x bd before meals	Tab Paracetamol (500mg x2) xbd After meals
Rescue Medication	60 days oral	Yogaraja Guggulu Pill (500gms x2) xbd before meals	Tablet Ibuprofen (200mg x2) xbd After meals
Follow up after very two week for three months (no intervention)			

Storage, packaging, and dispensing of investigational drugs

Decoction, paste and pottani will be manufactured and other drugs will be purchase from Sri Lanka Drug cooperation and Ayurveda Drug cooperation. Decoction, paste and pottani drugs used for study will be prepared at the Pharmacology department of IIM under GMP conditions. Decoction drugs, pottani, pills, tablets will be packed in light and waterproof polythene and pottani will be packed in light and waterproof sealed plastic container. Each drug will be packed for 14 days and labeled which indicate the cord number, arm, dose, time of administration, mode of administration (oral or external use etc.). These will be stored in the clinic of the Ayurveda Teaching Hospital, Sri Lanka, to be provided to randomized patients according to the predetermined allocation sequence. A supply of drugs for 14 days will be dispensed to the study participants at two weekly visits with instructions and patient diary will be provided for all.

Outcome Measurements

Primary Outcome

The primary endpoint is a change in the score on the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) measured at the baseline and the end of the intervention (after 8 weeks and 1 month of follow-up).

Secondary Outcome

Secondary outcome measurements will use WOMAC subscales, a pain disability index, a visual analog scale for pain and sleep quality, a quality-of-life index measured at the baseline and the end of the intervention (after 8 weeks and 1 month, 2month and 3 month of follow-up).

Changes in ESR and CRP count will be studied by comparing before and after treatment values. Procedures related to the study are shown in Table 2

Table 2 Study procedures

Study Period														
	Screening Run in Period	Recruitment	Treatment								Follow-up			
Time point (Weeks)	-1	0	1	2	3	4	5	6	7	8	12	16	20	
Eligibility Screening	+													
Informed Consent	+													
Recruitment		+												
Randomization			+											
Arms														
Arm I -STM														
Arm II Conventional														
Investigations	+		+							+	+	+	+	
Assessments														
WOMAC	+		+							+	+	+	+	
KOOS	+		+							+	+	+	+	
Pain Disability index	+		+							+	+	+	+	
Visual Analog Scale for pain	+		+							+	+	+	+	
Sleep Quality	+		+							+	+	+	+	
Quality-of-life index	+		+							+	+	+	+	
Adverse Events			+	+	+	+	+	+	+					

Safety Assessment

Each patient will undergo hematological and biochemical investigations (FBS, FBC, Lipid Profile, ESR, CRP, AST/ALT, and serum creatinine and 5ml blood will be drawn), urine full report before and after the

interventions which are done primary for safety assessment.

All adverse events experienced by patients will be recorded regularly after two weeks by the investigators at every visit to the clinic. Further, patients will be advised to record any adverse reactions in their patient diaries and will be advised to inform the investigators using the given contact numbers. They will also be advised to come to the clinic for assessment when they have any unexpected symptoms or complaints. If any serious adverse events occur, they will be carefully assessed and reported to the ERC of IIM within 5 working days. No serious adverse reactions are expected with any of the two study medications. However, in the events of an adverse reaction requiring in-hospital management, the facilities and expert management would be provided and the complete clinical trial will be terminated prematurely if there is evidence that the safety of the trial participants can no longer be assured or new scientific information arises during the course of the clinical trial regarding patient safety.

Data handling, record keeping, and dissemination

An individual file for each participant will be used to archive a hard copy of the case record forms including informed consent, results of heamatological and biochemical investigations, results of the physical examinations, and completed questionnaires.

The data will be retained with the researchers alone and will not be handed over to any other party under any circumstance. The data sheets will be kept under lock and key until the database is created. As soon as the database is created, burning will destroy the datasheets. This will approximately take 6 months from the onset of data collection.

Data will be entered by a minimum number of dedicated staff and saved in a dedicated computer with password protection. The study participant's information will be securely stored at each clinic visit during the study. At the end of the study, all records will continue to be kept in a secure location for a 2-year period. Study participants' data will be stored at the Institute of Indigenous Medicine, which will be used for statistical analysis and scientific reporting. Each participant's contact or identifying information will be separately stored. Individual participants and their research data will be identified by a unique study identification number. At the end of the study, all study databases will be de-identified and archived. A data safety monitoring board has been appointed according to the guidelines of Ethics Review Committee of IIM for safety monitoring. The board consists of three independent expert members. Further, we have no planned the auditing of this clinical trial, because it is a single – center trial involving 86 patients. The results of the study will be used for scientific reporting in conferences and will be published in peer - reviewed journals. Further results of the study and the grouping information of the participants will be provided to the individual after completion of the trial.

Ethical Considerations

The approval of the research protocol has been obtained from the research approval committee of the Faculty of Graduate Studies, University of Colombo and the Ethics Review Committee od the Institute of

Indigenous Medicine, University of Colombo. The trial was registered in ISRCTN registry (Trial Number ISRCTN58050062 https://doi.org/10.1186/ISRCTN58050062). The study will be conducted adhering Good Clinical Practice (GCP) guidelines. Protocol modifications will be informed to Ethics Review Committee and the trial registry approval.

Patients will be provided with an information sheet with the details of the research given in all three languages (Sinhala/Tamil/English) and written consent will be obtained before participation. The information provided will include the nature, duration, and possible consequences of the trial. A patient may withdraw his or her consent to participate in this study at any time, with no penalty or effect on medical care or loss of benefits. The questionnaire will be interviewer – administrated and anonymous. A minimal amount of data needed to assess the socio demographic data will be gathered. This will include occupation and nature of health condition. Researchers will not collect any other personal data.

Method of Data Analysis

For primary and secondary outcome measures, the mean values at baseline and at the end of the study and mean differences will be compared between the two arms using depending on the normality of the data. Within each treatment arm, the difference in the primary and secondary outcome measures before and after the intervention period will be compared. 95% confidence intervals will be calculated for all outcome measures that are normally distributed. Categorical variables will be compared between groups using the chi -square test.

Statistical analysis will be performed using the SPSS statistical Package program (Version 18), and the level of significance will be established at a =0.05. Missing data at outcome assessment will be replaced with the available latest values of the outcome measure. Intention -to -treat analysis will be performed for all efficacy outcomes and safety outcomes. In addition, per – protocol analysis will be performed for the efficacy outcomes by including only the patients completing the follow – up.

Discussion

Knee OA is a chronic joint disease with significant health and psychological burden to patients due to persistent pain for prolonged period. Calcium pyrophosphate dehydrate (CPPD) crystal deposition in association with OA is most common at the knee. This may result in more overt inflammatory component (stiffness, effusions) and superadded acute attacks of synovitis which predicts more rapid radiographic and clinical progression (25–28). OA accounts for 24% of all years lived with disability (YLD) and have been ranked as the 10th leading contributor to global YLDs. The global prevalence of hip and knee OA is approaching 5% and projected to increase the population ages. Additionally, job related indirect costs due to loss of productivity have been estimated cost from $ 3.4 to $ 13.2 billion per year. Recent guidelines have addressed the many treatments that aim to relieve symptoms, in particular pain and improved function and not provide a cure for OA. There are numerous drug treatments for osteoarthritis; however, their efficacy and adverse effect profiles often limit their use. Currently pharmacological, non-pharmacological and surgical measures are considered in treatment of OA with aims of reducing pain

and improving function of the knee joint. But pharmacological and non-pharmacological measures were still unable to address the structural deterioration of the effected joint. At present there is no proven disease-modifying therapy available for OA. During the drug approval process of structure modifying drugs allowing the use of surrogate markers which may be reasonably likely to predict important clinical outcomes, would increase the potential for the development of therapies of OA where currently there is no known cure and no interventions available to stop the progression or manage the symptoms with an acceptable benefit to harm profile (7). Therefore, effective treatment would be important for treating this disease. Due to fear of side effects and adverse effects of these allopathic treatment, presently most of them interest focused towards CAM and in Sri Lanka also many of the people seeking treatment regimens for knee OA from Sri Lankan Traditional medicine. Rasandivgunabhagasya decoction is a herbal decoction that has been prescribed for Knee OA with Yogaraja Guggulu as an internal medicine and Kumburuatadi pottaniya and Sandivadam lepaya were used for external local application in Sri Lankan Traditional medicine as a treatment regimen for a long time. Our research team designed these two arms, open labelled parallel group randomized control trial to compare and evaluate the effectiveness of this regimen in knee OA compared to pain management done with nonsteroid anti-inflammatory drug treatment regimen. This clinical trial will be able to provide evidence- based scientific data on the Sri Lankan Traditional Medicine regimen in the treatment of Knee OA. This trial is alos expected to develop the capacity to scientifically evaluate Sri Lankan Traditional Medicine treatment regimens that could help patients having chronic joint disorders such as Knee OA.

Strengths And Limitations

To our knowledge, this is the first randomized controlled clinical trial to investigate the efficacy of the Sri Lankan Traditional Medicine regimen in Sri Lanka for Knee OA. Results of this study will provide evidence regarding the use of this Sri Lankan Traditional Medicine regimen for treatment in knee OA. Any drugs containing heavy metals as ingredients cannot be used directly for human trials due to ethical issues. Therefore, only the herbal plant-based drug formulae were selected for the study.

Trial Status

The recruitment is currently in progress and it is expected that the recruitment will be completed by the end of August 2022.

Declarations

Availability of data and materials

After the study is completed, the data will be made available on request from the corresponding author.

Contributions

The study was conceptualized by PKP and HDS. The protocol was developed by HDS, PKP and SJ. Statistical advice and sample size calculation and method of analysis were provided by SDSW. Clinical trial conduct by all the investigators collectively. All authors read and approved the final manuscript.

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

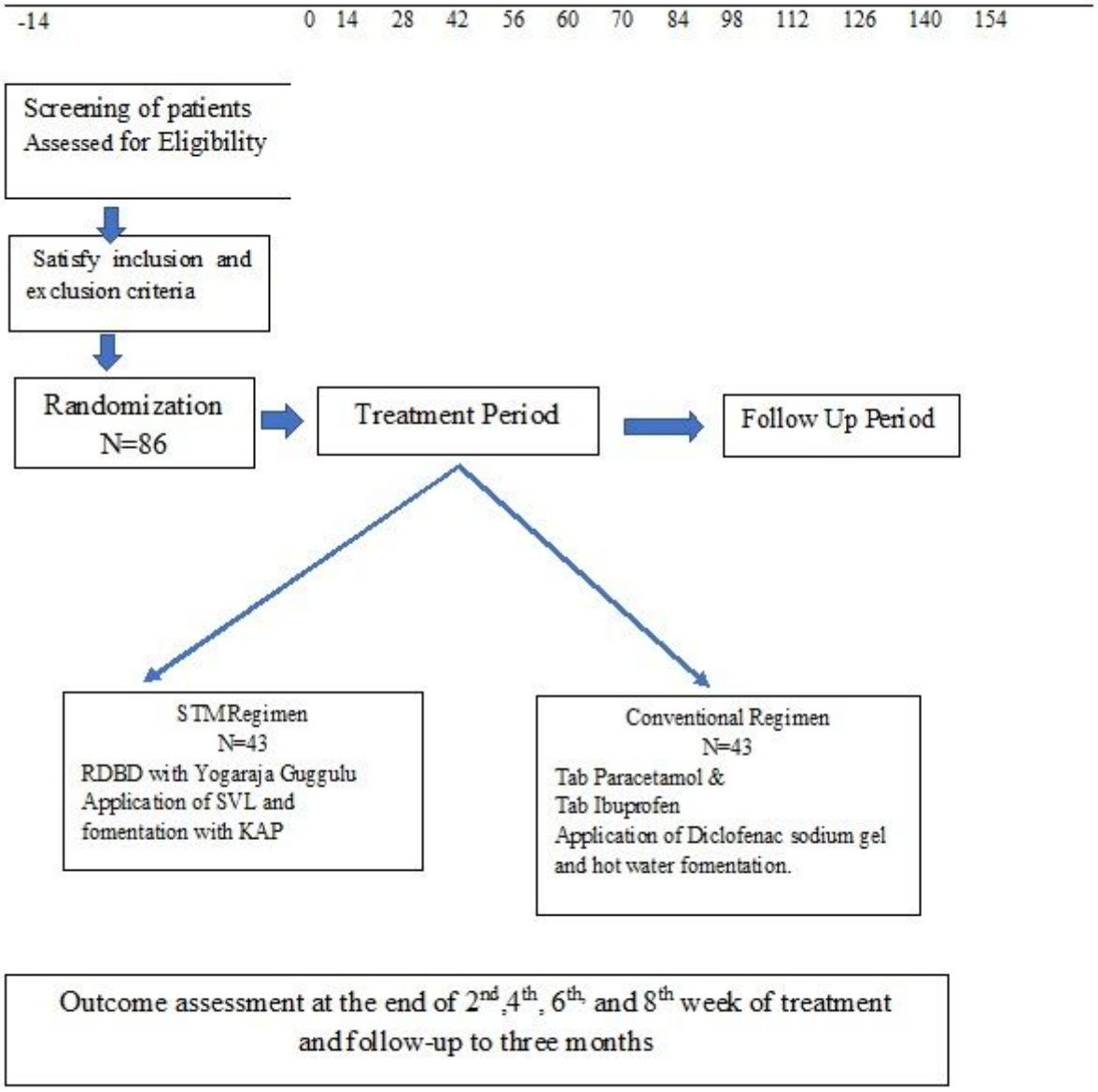

Figure 1

Flow chart of study design

Supplementary Files

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